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37 C.F.R. 1.8

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February 28, 2002
Date

Mark T. Garrett

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Zhang, et al

Serial No.: 09/413,109

Filed: October 6, 1999

For: METHODS FOR THE ADMINISTRATION OF ADENOVIRUS p53 (AS AMENDED)

Group Art Unit: 1636

Examiner: Guzo, D.

Atty. Dkt. No.: INRP:087/GNS

DECLARATION OF DEBORAH R. WILSON, PH.D, UNDER 37 C.F.R. 1.132

BOX AF
Commissioner of Patents
Washington, D.C. 20231

I, Deborah R. Wilson, Ph.D, declare that:

1. I am the Associate Vice President of Clinical Research at Introgen Therapeutics, Inc. ("Introgen"), assignee of the above-captioned application. I have been employed at Introgen for 7 years and was recently named Associate Vice President. My responsibilities as Associate Vice President of Clinical Research at Introgen include clinical science, pharmacokinetics, and drug safety. I am a citizen of the United States of America, and I reside at 11022 Silkwood, Houston, Texas 77031.

2. I understand that the Patent and Trademark Office has rejected claims in the above-referenced case as lacking enablement, based on reasons related to the lack of success of gene therapy.

3. Introgen and its collaborators have been conducting research and development of an Ad-p53 composition for the treatment of cancer for at least 10 years. Introgen's research and development has progressed to the point where its Ad-p53 composition, INGN 201 (Introgen's Advexin® adenovirus p53 product), which is disclosed in the present application, is involved in a number of clinical trials for head and neck cancer, lung cancer, breast cancer, esophageal cancer, glioma, prostate cancer, advanced solid tumors, bladder cancer, and ovarian cancer. *See* Table of Adenovirus-p53 Clinical Trials (Exhibit 1). INGN 201 is in phase III clinical trials for head and neck cancer. Phase II clinical trials are underway or have been completed for head and neck cancer, esophageal cancer, breast cancer, and non-small cell lung carcinoma. INGN 201 was used or has been approved for phase I clinical trials for lung cancer, breast cancer, liver cancer, glioma, prostate cancer, head and neck cancer, bladder cancer, ovarian cancer, colorectal cancer, malignant ascites, and solid tumors from a variety of origins.

4. Several clinical trials have been conducted for various cancers including ovarian cancer, lung cancer, bladder cancer, and metastatic colorectal cancer using a different Ad-p53 construct from another company, Schering Plough.[1]

5. The clinical trials discussed in paragraphs 3 and 4 involved or will involve a variety of administrations of Ad-p53 constructs. Administrations include: intraperitoneal,

[1] *See, e.g.*, Barnard (2000); Horowitz (1999); Kuball *et al.* (2002); Schuler *et al.* (2001) and the reference of Wills *et al.*, which provides the details regarding the structure of the SCH 58500 Ad-p53 construct, which lacks protein IX. (Exhibit 2)

intravenous, intravesical, intratumoral, intramucosal injection, oral rinse, and broncho-alveolar lavage.

6. I anticipate Introgen will proceed with other clinical trials in the future involving adenovirus-p53 constructs, given the success I have observed in the ongoing or previous clinical trials with Introgen's product, INGN 201.

7. I declare that all statements made herein of my own knowledge are true, and that all statements of my own belief are believed to be true, and further that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under § 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this patent, and any reexamination certificate issuing thereon.

27 February 2002
Date

Deborah R. Wilson, Ph.D.

Table of Adenovirus-p53 Clinical Trials (as of February 2002)

Treatment	Cancer	Admin	Clinical Stage	Status/Result
INGN 201	SCCHN (T302)	Intratumoral	III	Ongoing
INGN 201	SCCHN (T301)	Intratumoral (with chemotherapy)	III	Ongoing
INGN 201	NSCLC	Intratumoral (with radiation therapy)	II	Combination INGN 201 and radiation therapy appears more effective than radiation alone
INGN 201	SCCHN (T207)	Intratumoral	II	Safe
INGN201	Locally advanced primary breast	Intratumoral (with chemotherapy)	II	Study has been initiated
INGN 201	Esophageal	Intratumoral	II	Ongoing
INGN 201	SCCHN (T201)	Intratumoral	II	Safe; demonstrated clinical activity
INGN 201	SCCHN (T202)	Intratumoral (lower dose)	II	Safe; trend towards shorter survival than T201
INGN 201	Ovarian	Intraperitoneal	I	Transgene expression observed and increased expression of downstream marker; well-tolerated
INGN 201	Ovarian	Intraperitoneal (laparoscopy)	I	Well-tolerated; potentially useful clinical response
INGN 201	Bladder	Intravesical	I	Transgene expression observed; safe; ongoing
INGN 201	Advanced solid tumors (colon, breast, prostate, sarcoma,	Intravenous	I	Well tolerated at doses up to $1x10^{12}$ vp; accrual is ongoing to further

	NSCLC, H&N)			determine MTD; evaluation of p53 expression is pending
INGN 201	SCCHN	Intratumoral (with and without tumor resection)	I	Transgene expression and expression of downstream targets observed; safe; potentially useful clinical response
INGN 201	NSCLC	Intratumoral	I	Transgene expression and apoptosis observed; safe; potentially useful clinical response
INGN 201	NSCLC	Intratumoral (with cisplatin)	I	Expression observed; well tolerated; potentially useful clinical response
INGN 201	Prostate	Intratumoral (INGN 201 treatment prior to tumor resection)	I	Transgene expression and apoptosis demonstrated; safe
INGN 201	Glioma	Intratumoral and intracranial (stereotactic injection intratumorally, followed by tumor resection, followed by injection into tumor bed	I	Expression observed; safe; apoptosis observed; ongoing
INGN 201	Hepatocellular Carcinoma	Intratumoral	I	Study closed; 1 patient treated
INGN 201	Breast	Intratumoral (with chemotherapy)	I	Study closed; 2 patients treated

INGN 201	Bronchioloalveolar lung carcinoma	Broncho-alveolar lavage	I	Safe; potentially useful clinical response; ongoing
INGN 201	Malignant ascites	Intraperitoneal	I	Study closed; 1 patient treated
INGN 201	Colorectal	Intratumoral	I	Study closed; 6 patients treated; expression of downstream markers demonstrated
INGN 201	Lung	Intratumoral (with and without cisplatin)	I	Ongoing
INGN 201	Oral dysplasia (premalignant)	Intramucosal injection; oral rinse		Not started
SCH 58500	Ovarian	Intraperitoneal (with chemotherapy)	II/III	Reported closed
SCH 58500	Lung	Intratumoral (with chemotherapy)	II	Transgene expression observed; well-tolerated; enhanced local effects suggested with certain chemotherapies
SCH 58500	Ovarian	Intraperitoneal (with chemotherapy)	I/II	Well tolerated; expression observed; prolonged patient survival
SCH 58500	Lung	Intratumoral	I	Transgene expression and expression of downstream target observed; safe; transient tumor growth control
SCH 58500	Bladder	Intratumoral or intravesical (with	I	Transgene expression and expression of downstream marker

		transduction enhancer)		demonstrated after intravesical instillation